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## MINIREVIEW

### How Does Residual Water Affect the Solid-State Degradation of Drugs in the Amorphous State?

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#### Introduction

It is widely recognized in the pharmaceutical field that exposure of solid drugs (small molecules or proteins) to high relative humidity and the resulting association of water vapor with the solid generally accelerate the rate of chemical degradation.<sup>1</sup> Although there are true solid-state reactions that take place only in the crystalline state or to a much lesser extent in the liquid or solution state than in the crystal,<sup>2,3</sup> most instabilities observed for drugs occur in solution much more readily than in the solid state; when they do occur over practical time scales in the solid state, it is very likely that the reaction is taking place in the more disordered amorphous regions of the solid.<sup>4</sup> Indeed, it has been shown in a number of cases that under otherwise identical conditions reactivity of a particular substance in the amorphous state is greater than that in the crystalline state.<sup>5–8</sup>

Generally, for reactions occurring in the amorphous solid state, the rate of reactivity increases with increasing water content, and this can be attributed to the ability of the amorphous solid to absorb water vapor into its bulk structure, forming an amorphous solution.<sup>9,10</sup> In a few cases it has been reported that a certain amount of water must be present to ensure chemical stability, e.g., lipid peroxidation rates decrease with the addition of small amounts of water;<sup>11,12</sup> however, a destabilizing effect of absorbed water is more generally the case for the major types of drug degradations, e.g., hydrolysis, oxidation, or deamidation.

An examination of the literature indicates that discussions concerning solid-state reactivity in the amorphous state have followed along two lines. In some work correlations appear to exist between the rate of reactivity and the glass transition temperature,  $T_g$ , strongly supporting the role of water as a plasticizer in facilitating chemical reactivity by increasing molecular mobility.<sup>13,14</sup> In other studies, a lack of correlation with  $T_g$ <sup>15</sup> and reactivity well below  $T_g$ <sup>16</sup> has been shown to occur, and there also appears to be a better correlation of reactivity with water activity,  $a_w$ , defined as:

$$a_w = p/p_o \quad (1)$$

where  $p_o$  is the vapor pressure of liquid water at temperature,  $T$ ,  $p$  is the vapor pressure of water in the system containing the solid, and  $p/p_o \times 100$  is taken as the relative humidity, RH. The use of  $a_w$  as a point of reference with regard to the role of water is convenient since through the water vapor absorption isotherm a relationship between  $a_w$  or RH and water content can be established. However, the use of such a parameter, in itself, provides limited physical insight into the actual mechanistic role of water at a particular water content.<sup>17</sup> Consequently, in this minireview we briefly examine in more quantitative terms how water can affect chemical reactions in the solid amorphous state, offering a means by which one can characterize the relative role of different possible effects in a more quantitative manner.

#### General Considerations

In attempting to discuss the role of water in affecting chemical reactivity, we can consider two parameters, the maximal extent of degradation and the rate of degradation. From a pharmaceutical perspective, the maximal extent of the reaction is not a critical factor given the limited degradation normally allowed over the shelf life of the drug substance. However, attention to this parameter, coupled with the rate of the reaction, can provide some important insights for later discussion. For reversible reactions, the extent of conversion can be determined from a knowledge of the equilibrium constant. (See ref 18 for details.) For example, for reaction



the equilibrium constant,  $K$ , can be represented as

$$K = \frac{a_C a_D}{a_A a_B} = \frac{(X_C X_D) (\gamma_C \gamma_D)}{(X_A X_B) (\gamma_A \gamma_B)} \quad (3)$$

where  $a_C$ ,  $a_D$ ,  $a_B$ , and  $a_A$  are the activities of products and reactants;  $X_C$ ,  $X_D$ ,  $X_B$ , and  $X_A$  are the concentrations of

products and reactants; and  $\gamma_C$ ,  $\gamma_D$ ,  $\gamma_B$ , and  $\gamma_A$  are the corresponding activity coefficients.

It should be noted that such thermochemical concepts traditionally have been applied for solution reactions (e.g., see refs 18 and 19) and inorganic solid-state reactions (e.g., ref 20). Recently, such a thermodynamic description has been extended to organic solid-state reactions.<sup>21,22</sup>

If water is one of the reactants or products, the concentration or activity of water must be included in the above equation, and a change of water activity or concentration will directly influence the maximal extent of the reaction. If water does not participate as a reactant or product, a change in water content can influence the extent of degradation through an indirect effect on the activities of the various reactants and products.

The general rate of the reaction,  $V$ , presented above can be represented in terms of the consumption of chemical,  $A$ , in the form

$$V = -\frac{dA}{dt} = k f(X_A X_B) \quad (4)$$

where  $f(X_A X_B)$  indicates some function of  $X_A X_B$  and  $k$  is the rate constant. The rate of the reaction therefore can be affected in two ways: (1) by changing the concentration of reactants without affecting  $k$  and (2) by changing  $k$ . Obviously, some reactions can be more complex, involving a number of intermediate reactions with corresponding rate constants, but the principles discussed below will be applicable to any of the rate-determining steps.

From our understanding of solution chemistry, we know that a change in the composition of the reaction medium (solvent) can cause a change in  $k$  and that there are two possible types of medium effects relevant to this discussion. For reactions under kinetic control, from transition-state theory,<sup>23</sup> we can write

$$k = \frac{RT}{N_A h} \exp\left(-\frac{\Delta G^\ddagger}{RT}\right) \quad (5)$$

where  $R$  is the universal gas constant,  $T$  is absolute temperature,  $N_A$  is Avogadro's number,  $h$  is Planck's constant, and  $\Delta G^\ddagger$  is the Gibbs free energy of activation. In such a case the influence of the medium on  $k$  will be through an effect on the Gibbs free energy of the reactant, activated complex, or both. A number of more or less empirical relationships connecting certain physicochemical characteristics of a solvent and the rate constant,  $k$ , are available (e.g., ref 24).

For reactions involving two species under diffusion control (very likely to be important in the amorphous solid state), the rate constant  $k$  can be expressed as<sup>25</sup>

$$k = 4\pi d^* D_r N_A \quad (6)$$

where  $d^*$  is a collision diameter,  $D_r$  is the diffusion coefficient of the reactants, and  $N_A$  is Avogadro's number. A possible medium effect in this case would be through an effect on the diffusion coefficient,  $D_r$ , or, in other words, through an effect on molecular mobility.

Thus, from these simple considerations we can see at least four ways by which residual absorbed water can affect chemical stability in the amorphous state. First, water can act as a direct reactant with the drug and, hence, influence the rate of the reaction through its concentration and the maximal extent of reaction through its activity. This would be true, for example, in various hydrolytic reactions. Second, water may impact on chemical reactivity as a product of the reaction, likewise through its activity by having an inhibiting effect on the extent of the forward reaction. Examples of reactions producing water would include the Maillard reaction (nonenzymatic browning).<sup>26</sup> Third, water dissolved in the

Table 1—Content of Remaining Drug (Percent of Initial) for Reversible and Irreversible Reactions in Which Water is a Reactant

Water Content, % (w/w)	Irreversible MW 15 000 <sup>b</sup>	Irreversible MW 300 <sup>b</sup>	K = 10 <sup>a</sup>		K = 0.1 <sup>a</sup>	
			MW 15 000 <sup>b</sup>	MW 300 <sup>b</sup>	MW 15 000 <sup>b</sup>	MW 300 <sup>b</sup>
0.1	16.6	98.3	31.5	98.3	78.1	98.5
1	0	83.2	1.3	83.5	42.4	91.4
3	0	48.5	0.4	52.7	23.4	83.0

<sup>a</sup>  $K$  is the equilibrium constant for the reversible reaction. <sup>b</sup> MW represents the molecular weight of the drug.

amorphous matrix can simply act as a medium (solvent) to influence the local polarity without directly participating in the reaction. Fourth, water by virtue of its solubility in the amorphous phase, its high free volume, and low  $T_g$  (135 K) can exert a very significant effect on the mechanical properties of the solid as a plasticizer, reducing viscosity and therefore enhancing diffusivity.<sup>9,13</sup>

## Numerical Examples

To provide some basis for assessing the relative contributions of the various modes by which water can affect reactivity in the amorphous state, we provide below some numerical examples with respect to an expected effect from each mode under typical conditions. Although such estimates must be very approximate, we believe that they provide a basis for a more realistic discussion about the most important roles that water plays in such drug degradation.

**Water as a Reactant**—Let us consider the hydrolysis of two preparations with molecular weight 300 and 15 000 at 0.1%, 1%, and 3% residual water content and calculate the molar percent of remaining drug as a function of initial water content for an irreversible reaction and for a reversible reaction (eq 2) with  $K$  equal to 10 or 0.1. (Note that such values are reasonable in practical terms, as in the case of acid-catalyzed hydrolysis of some acids where  $K$  is 0.15–0.40.<sup>27</sup>) In this calculation we assume that  $(\gamma_C \gamma_D)/(\gamma_A \gamma_B)$  in eq 3 is equal to 1, as has been discussed.<sup>19</sup> Details of the calculation of the maximal equilibrium conversion can be found, for example, in ref 18. As shown in Table 1, and as expected, the more water that is present in the system the greater the extent of the reaction. We can also see how  $K$  and the molecular weight can influence the extent of the reaction at the same initial water content. In the case of the irreversible reaction, a critical extent of conversion, e.g., 10% degradation, for the high molecular weight preparation, e.g., a protein, will be achieved at only 0.012% of water content; whereas for the low molecular weight preparation, the critical water content is 0.6%. If the reaction is reversible, the critical water content can be higher. For example, for the low molecular weight preparation at  $K = 0.1$ , maximal degradation will be less than 10% at a 1% water content.

With regard to the effect of initial water content on the rate of reactivity,  $V$ , by direct involvement in the reaction, we can see through the rate equation below (assuming an irreversible biomolecular reaction) that

$$V = k[W][A] \quad (7)$$

where  $[W]$  is the water concentration, that the rate will be proportional to the water concentration and that the rate will increase 10- and 30-fold with a corresponding increase in water content from 0.1% to 1% and 3%, respectively.

**Water as a Product**—If water is produced during the course of a reaction, it can be expected to possibly contribute directly to the reaction or indirectly through medium effects to be described in more detail below. With regard to more direct effects on the reaction, if water is a product of a

Table 2—Content of Remaining Drug (Percent of Initial) for a Reversible Reaction in Which Water Is a Product

Water Content, % (w/w)	$K = 10^a$		$K = 0.1^a$	
	MW 15 000 <sup>b</sup>	MW 300 <sup>b</sup>	MW 15 000 <sup>b</sup>	MW 300 <sup>b</sup>
0.1	2.1	3.7	68.0	71.9
1	17.9	20.3	95.6	95.6
3	85.5	87.3	99.8	99.8

<sup>a</sup>  $K$  is the equilibrium constant for the reversible reaction. <sup>b</sup> MW represents the molecular weight of the drug.

Table 3—Rate Constants Relative to the Rate Constant at Zero Water Content for Reactions in Organic Solvents at Different Water Contents

No.	Reaction	0% Water	2% Water	5% Water	10% Water	20% Water	Ref
1a	Solvolysis of <i>t</i> -BuCl	1	1.87	4.14	12.9	66	28
1b	Nucleophilic substitution, unimolecular <i>t</i> -BuBr	1				66	29
2	Nucleophilic substitution, bimolecular $\text{MeS}^+ + ^-\text{OH}$	1				0.025	29
3	Nucleophilic substitution, unimolecular <i>t</i> -Bu <sup>+</sup> SM <sub>2</sub>	1				0.65	29

Table 4—Rate Constants Relative to the Rate Constant at 0.1% of Water for the Reactions from Table 3

Water Content, %	No. 1 <sup>a</sup>	No. 2 <sup>b</sup>	No. 3 <sup>c</sup>
0.1	1	1	1
1	1.3	0.98	0.5
3	2.5	0.96	0.17

<sup>a</sup> Column no. 1: charge density of the transition state is greater than that of the reactant state. <sup>b</sup> Column no. 2: charge density of the transition state is about the same as for the reactant state. <sup>c</sup> Column no. 3: charge density of the transition state is lower than that of the reactant state.

particular reaction, its presence would be expected to be an inhibitor of the reaction, unless the reaction is irreversible. Table 2 gives the amount of remaining drug at maximal reactivity for a reversible reaction, calculated for two equilibrium constants and three initial water contents where the reaction is between a drug (molecular weight either 300 or 15 000) and an excipient (molecular weight 324), both in a matrix of inert amorphous diluent polymer with a polymer/excipient drug weight ratio of 90/9/1. It can be seen that molecular weight does not have any significant effect on the extent of the reaction opposite to what we saw with water as a reactant (see Table 1), but there is a significant inhibiting effect with increasing initial water content and an increase in the value of  $K$ .

**Water as a Medium**—It is well recognized that a reaction rate for the same reaction can differ significantly when carried out in different solvents that do not directly become involved in the reaction as reactants or products. As can be seen in Table 3, for a few examples from the literature, increasing water content (increasing solvent polarity) from 0% to 20% can greatly increase some reactions (reaction 1), decrease others (reaction 2), and have very little effect on others (reaction 3). Table 4 shows how increasing the water content from 0.1% to 1% and 3% changes the relative rate constants for each of the reactions given in Table 3. These relative rate constants were obtained by linear interpolation of the data in Table 3. What we can conclude from this analysis is that medium effects due to residual water in the amorphous state can be significant, but that the direction and extent of this effect will depend on the nature (e.g., polarity, specific solvation) of the transition state for the particular reaction causing degradation.

**Water as a Plasticizer**—As mentioned above it is very likely under some conditions particularly near to and below  $T_g$  that reactions taking place in the amorphous state will be limited by the molecular mobility of all reactants. Consequently, we can expect residual water to play some role as a plasticizer in such cases. To assess this effect more quantitatively, it would be desirable to be able to estimate the effects of absorbed water on the molecular mobility of the drug and other reactants participating in the reaction.

Molecular mobility can involve translational or rotational motions of entire molecules, or segments of macromolecules, as well as intramolecular motions involving specific portions of the molecule, e.g., methyl group rotations. The translational and rotational motions of most molecules in single- or multiple-component systems, as reflected in the diffusion coefficient, are generally strongly coupled to shear viscosity,  $\eta$ .<sup>30</sup> If, however, one species is much smaller than the matrix molecules within which diffusion takes place, diffusion will be more weakly coupled,<sup>31</sup> as most likely will be intramolecular motions. For this discussion and for illustrative purposes, let us consider the most general situation where a reaction between two substances is diffusion-limited such that the relationship between the translational diffusion coefficient  $D_r$  and shear viscosity  $\eta$  is given by the Stokes-Einstein equation

$$D_r = \frac{kT}{6\pi\eta r} \quad (8)$$

where  $r$  is the molecular radius,  $k$  is the Boltzmann constant, and  $T$  is temperature. In actuality for amorphous materials near the glass transition temperature, measured diffusion coefficients generally have values greater than predicted from eq 8, being proportional to  $\eta^{-\xi}$  rather than  $\eta^{-1}$  with values of  $\xi$  generally being less than 1.<sup>32</sup> If we assume that the reaction rate constant  $k$  is proportional to the diffusion coefficient  $D_r$  (eq 6), we can then express the relative change in  $k$  as

$$\frac{k_2}{k_1} = \frac{D_{r2}}{D_{r1}} = \left(\frac{\eta_1}{\eta_2}\right)^\xi \quad (9)$$

where the subscripts 1 and 2 represent zero water content and hydrated sample, respectively. Hence, knowing how absorbed water changes  $\eta_1$  to  $\eta_2$  can give us the ratio  $k_2/k_1$ .

A number of equations describing the temperature dependence of viscosity for amorphous systems are available. (For a review, see ref 33.) Most of them, based on free volume theory, use a reference temperature, e.g.,  $T_g$  in the Williams-Landel-Ferry equation or  $T_0$  in the Vogel-Tamman-Fulcher (VTF) equation. We will use the VTF equation (eq 10 below) since it allows us to describe viscosity below  $T_g$ , where many reactions of pharmaceutical interest can take place. Thus, at temperature  $T$  in units of Kelvin

$$\frac{\eta}{\eta_0} = \exp\left(\frac{DT_0}{T - T_0}\right) \quad (10)$$

where  $\eta_0$  is the viscosity of the system as  $T \rightarrow \infty$ ,  $\eta$  is the viscosity at temperature  $T$ ,  $T_0$  is the temperature at which  $\eta$  becomes effectively infinite, and  $D$  is a constant characteristic of the fragility of a particular amorphous material, i.e., the manner in which viscosity changes with temperature (to be discussed).<sup>34</sup> It has been further shown<sup>34</sup> that at  $T = T_g$ , one can rewrite eq 10 as

$$\frac{T_g}{T_0} = 1 + \frac{D}{[2.303 \log(\eta_g/\eta_0)]} \quad (11)$$

where  $\eta_g$  is the viscosity at  $T_g$ . It has been shown for many systems that  $\log(\eta_g/\eta_0)$  is equal to about 17,<sup>34</sup> and therefore we can estimate  $T_0$  knowing  $T_g$  and  $D$  from

Table 5—Effect of Water on the Relative Rate Constants for Diffusion-Controlled Reactions at 30 °C as a Function of Fragility ( $D$ )<sup>a</sup>

Water Content, % (W/W)	$T_g$ , °C	$D = 10$		$D = 30$	
		$T_o$ , °C	$k_2/k_1$ <sup>b</sup>	$T_o$ , °C	$k_2/k_1$ <sup>b</sup>
0	75	4.1	1	-76.1	1
0.1	74.3	3.6	6.4	-76.1	1
1	68.1	-1.5	$4.8 \times 10^8$	-80.0	9.5
3	55.1	-11.7	$3.1 \times 10^{14}$	-87.3	475

<sup>a</sup> The materials have the same dry  $T_g$  and  $T_g$  vs water content profiles ( $K = 0.3$  in the Gordon-Taylor Equation). <sup>b</sup>  $\xi = 0.75$ <sup>32</sup> (incomplete coupling between  $D$  and  $\eta$ ) has been used in the calculation of  $k_2/k_1$  (eq 9); at  $\xi = 1$  (complete coupling between diffusion coefficient and viscosity) the water effect is even more considerable.

$$T_o = \frac{T_g}{\left[1 + \frac{D}{(2.303(17))}\right]} \quad (12)$$

and in turn calculate  $\eta$  from eq 10, at any water content associated with a particular value of  $T_g$  produced due to the presence of water.

To estimate  $T_g$  for different water contents, we can use an equation that often has been successful in describing the  $T_g$  of a mixture of two components in terms of their individual  $T_g$  values,  $T_{g1}$  and  $T_{g2}$ , the Gordon-Taylor equation,<sup>9,35</sup> where

$$T_g = \frac{(w_1 T_{g1} + K w_2 T_{g2})}{w_1 + K w_2} \quad (13)$$

where  $w_1$  and  $w_2$  are weight fractions and  $K$  is a constant characteristic of the system.

To carry out our estimation of  $\eta_1/\eta_2$ , we will choose two amorphous systems having the same  $T_g$  in the dry form but exhibiting different responses to temperature change (degree of fragility<sup>34</sup>), as reflected in the value of  $D$  in eq 10. Most glass-forming materials of interest have values of  $D$  that fall in the range of 2–100.<sup>34</sup> A value of 30 would represent the expected fragility of a protein,<sup>36</sup> while a value of 10 would be reasonable for a small molecule like indomethacin.<sup>37</sup> We will further assume, as has been shown for a few systems,<sup>36</sup> that the fragility of a solid ( $D$ ) does not change significantly with water content. Furthermore, we will choose a Gordon-Taylor constant,  $K$ , equal to 0.3, since its value generally falls in a range 0.15–0.35,<sup>38</sup> and a  $T_g$  for the dry amorphous material of 75 °C or 348 K, a reasonable value for a small molecule.

Table 5 gives  $T_g$ ,  $T_o$ , and the relative rate constants at 30 °C,  $k_2/k_1$  equal to  $(\eta_1/\eta_2)^\xi$ , with  $\xi = 0.75$ , as a function of water content for a material having  $K = 0.3$  and  $D = 10$  or 30. It can be seen in the fourth and sixth columns that increasing the water content by only a few percent of water can increase a diffusion-limited reaction by several orders of magnitude through its plasticizing effects and that this effect can be quite different depending on the value of  $D$  for the solid: the more fragile the system (smaller  $D$  values) the greater the effect of water on the reaction rate.

## Conclusions

In this minireview we have attempted to provide a basis for establishing the relative importance of different mechanisms by which water can influence the rates of reaction taking place in the amorphous state. The nature of the specific reaction will determine whether water acts as a reactant or product and whether water as a polar medium will increase, decrease, or have no effect on the reaction. In all cases we expect absorbed water to have some effect on the molecular mobility of the system and, hence, some effect on reactions requiring some molecular motion as a rate-limiting step. This certainly will be critical for any reaction involving

the translational diffusion of two or more reactants including water, but it may also play a role when certain rotational motions or intramolecular motions are critical for reactivity. Such effects should be particularly important if the reaction takes place at temperatures in the vicinity of  $T_g$  or below  $T_g$ . Critical to how significant this effect will be is the extent to which  $T_g$  is reduced by absorbed water and the intrinsic dynamic properties of the amorphous solid as reflected in its extent of fragility ( $D$ ) as defined in the VTF equation. Thus, we can conclude, for example, for systems with values of  $D$  in the range of 2–100 and with Gordon-Taylor constants of 0.15–0.35, that a 10-fold increase in water content from 0.1% to 1% for reactions where all potential effects of water would be operative would change the apparent rate constant as a reactant by a factor of 10, as a polar medium by a factor of 0.2–2 (in either direction), and as a plasticizer by a factor of  $10^1$ – $10^6$ . Consequently, to fully understand the relative importance of such effects on a particular solid-state reaction encountered during drug product development, it will be useful to study the reaction in solution close to those expected to occur in the amorphous state and to assess potential mechanisms involving water as a reactant or medium. It would then be useful to determine the various parameters associated with the solid amorphous state,  $T_g$ ,  $T_o$ ,  $D$ , etc. When other components, such as excipients (including buffers), are present, obviously, the characterization of these parameters will be more complex. However, it should be possible to make reasonable assumptions and approximations to establish a baseline for further experiments.

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